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AQ1 *N*-acetylcysteine as an Adjunct to Risperidone for Treatment of Negative Symptoms in Patients With Chronic Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Study

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AQ2 **Objectives:** Despite the burden of negative symptoms on quality of life in schizophrenic patients, no completely effective treatment has been developed to address such symptoms yet. Abnormalities in oxidative stress pathways have been recently demonstrated to be involved in the pathophysiology of schizophrenia, and a growing interest in antioxidant agents is emerging for targeting negative symptoms of schizophrenia. *N*-acetylcysteine (NAC) is a potent antioxidant with neuroprotective properties. This study aimed to evaluate the possible effects of NAC as an adjunct to risperidone in treating negative symptoms of schizophrenia.

Materials and Methods: In this randomized double-blind, placebo-controlled, parallel-group study, 42 patients with chronic schizophrenia with a score of 20 or greater on the negative subscale of positive and negative syndrome scale (PANSS) were enrolled in the active phase of their illness. The participants were equally randomized to receive NAC (up to 2 g/d) or placebo, in addition to risperidone (up to 6 mg/d) for 8 weeks. The participants were rated using PANSS every 2 weeks, and a decrease in PANSS negative subscale score was considered as our primary outcome.

Results: By the study end point, NAC-treated patients showed significantly greater improvement in the PANSS total ($P = 0.006$) and negative subscale ($P < 0.001$) scores than that in the placebo group, but this difference was not significant for positive and general psychopathology subscales. There was no significant difference between the 2 groups in the frequency of adverse effects.

Conclusions: *N*-acetylcysteine add-on therapy showed to be a safe and effective augmentative strategy for alleviating negative symptoms of schizophrenia.

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Negative symptoms in schizophrenia are characterized by deficits in normal emotion and social functions that can be primary or secondary to the illness treatment or other manifestations.[1] These symptoms are strongly associated with long-term disability tending to worsen over time and negatively affect patient quality of life.[2] Despite such burden, negative symptoms are more resistant to treatment than the positive ones are and present antipsychotics as incapable of relieving negative schizophrenic symptoms.[3] Because no fully effective treatment for these symptoms has been developed yet, many researchers are striving on to find novel therapeutic agents on the basis of underlying defects in schizophrenia. Several lines of evidence suggest that oxidative stress plays a key role in the pathophysiology of various neuropsychiatric disorders, and oxidative stress pathways have recently attracted greater attention as promising novel targets for treating these disorders.[4,5] Although numerous antioxidant agents with different pharmacokinetic and pharmacodynamic profiles are currently available, relatively few clinical trials have been designed, to date, to evaluate their probable beneficial effects on disorders affecting the central nervous system and higher cortical functions such as schizophrenia.

Glutathione (GSH) is one of the most important tissue antioxidants in the brain, which is composed of glycine, cysteine, and glutamate.[6] Glutathione is the main endogenous antioxidant produced by cells and directly neutralizes free radicals and reactive oxygen species.[7] Glutathione system dysfunctions have been illustrated in many neuropsychiatric disorders including schizophrenia.[8,9] Glutathione levels are decreased in blood samples, cerebrospinal fluid, and postmortem brains of schizophrenic individuals.[10–13] It has been demonstrated that GSH depletion exacerbates schizophrenic symptoms through increased oxidative stress and subsequent neuronal toxicity.[14,15] Besides its antioxidant and free radical scavenging properties, GSH can modulate the glutamate N-methyl-D-aspartate receptor (NMDAR) activity by decreasing oxidizing agents that bind to the redox-sensitive site of NMDAR complexes.[8,16] Glutathione deficits induce synaptic plasticity impairments and NMDAR hypofunction in rats.[17] The relationship between GSH and glutamate systems is particularly interesting in light of proven underlying dysfunctions of glutamate receptors and glutamatergic neurotransmission in schizophrenia.[18]

N-acetylcysteine (NAC), an acetylated derivative of amino acid L-cysteine, is a GSH precursor with antioxidant, neurotropic, and anti-inflammatory properties, along with modulatory effects on dopaminergic and glutamatergic systems.[19] Despite oral GSH, which is rapidly metabolized by the liver and the intestines and has poor penetration of the blood-brain barrier, AQ3 oral NAC is quickly absorbed from the alimentary tract, which leads to increased GSH plasma levels, and crosses the blood-brain barrier serving as a precursor for GSH synthesis in the central neurons.[20,21] Beneficial neuroprotective effects of NAC have been demonstrated in many preclinical and clinical studies.[19,22,23] In a 6-month double-blind, placebo-controlled, randomized trial, Berk et al[24] reported significantly greater improvement in negative symptoms of the schizophrenic individuals who received NAC than that in the placebo-treated patients. In another randomized, double-blind clinical trial with crossover design, treatment with NAC significantly improved mismatch negativity (MMN) compared with placebo in the patients with schizophrenia.[25] Moreover, low-dose add-on administration of NAC could significantly improve the symptoms in a young woman with treatment-resistant schizophrenia.[26] In addition to clinical improvement, it has been recently shown that NAC can modulate electroencephalographic synchronization in patients with schizophrenia.[27] Regarding the role of NAC in the oxidative balance and its beneficial regulatory effects on some impaired neurotransmission pathwaysin schizophrenia including glutamate, it can be hypothesized that NAC would be of benefit in schizophrenia, especially in alleviating the negative symptoms.[19] Because of inadequate response seen with current medications, there is a growing interest in adjunctive strategies with different agents for the treatment of schizophrenia or, at least, improving its disabling symptoms. Although some studies have shown the improvement of negative symptoms in schizophrenia by NAC, there is no published study regarding the short-term therapy with adjunctive NAC in negative symptoms of patients with schizophrenia in the active phase.[24] Therefore, we designed the present study to evaluate the efficacy and tolerability of NAC as an adjunctive therapy to risperidone in the treatment of negative symptoms of patients with schizophrenia and in the active phase.

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MATERIALS AND METHODS

Trial Design

This was an 8-week, parallel-group, placebo-controlled, double-blind clinical trial with equal randomization (1:1). The trial protocol was registered at the Iranian Clinical Trials Registry (IRCT201106031556N21; www.irct.ir). The study was approved by the institutional review board of Tehran University of Medical Sciences and performed in accordance with the Declaration of Helsinki and its subsequent revisions.

Participants

Inclusion Criteria

Male and female inpatients aged 18 to 50 years were eligible to participate in this study if they had a diagnosis of schizo- AQ5 phrenia based on the *DSM IV-TR* criteria, a minimum score of 60 on the PANSS, a score of 20 or greater on the PANSS negative subscale, and a minimum disease duration of 2 years (chronic schizophrenia), in addition to being in the active phase of their illness. Diagnosis was based on a Structured Clinical In- AQ6 terview for *DSM-IV-TR* Axis I Disorders (SCID) and was confirmed with chart review and senior physician interview.

Exclusion Criteria

We excluded patients with diagnosis of any other *DSM-IV* psychiatric disorder on the basis of a structured diagnostic interview. Patients with significant depression, defined as a score of 14 or greater on the 17-item Hamilton Depression Rating scale (HDRS) or a score of 4 or greater on depression item of PANSS, were also excluded from the study.[28] Other exclusion criteria were serious medical or neurological disorders, alcohol or substance (other than nicotine) dependence, mental retardation (intelligence quotient, <70), inability to communicate, history of hypersensitivity to NAC or risperidone, pregnancy, lactation, and hepatic or kidney disease. Women in reproductive age were included only if they were using a reliable contraception method. Patients were also excluded if they had received any oral antipsychotic drug during the last week, any depot antipsychotic medication during the last month, or electroconvulsive therapy (ECT) during the last 2 weeks before their enrollment. The participants were not allowed to use antidepressants, mood stabilizers, sedating antihistamines, or other antipsychotics during the course of this trial.

After a complete description of study details, written informed consent was obtained from the eligible participant and/or the legal representative. The patients were informed of their right to withdraw from the project at any time without any negative effect on their relationship with health care providers.

Study Settings

This study was a multicenter clinical trial conducted from July 2011 to February 2013 at 3 academic hospitals: Roozbeh Hospital (Tehran University of Medical Sciences, Tehran, Iran), Razi Hospital (University of Social Welfare and Rehabilitation Sciences, Tehran, Iran), and Qods Hospital (Kurdistan University of Medical Sciences, Sanandaj, Iran). Each participant was evaluated on 5 occasions: at the baseline/screening visit and at weeks 2, 4, 6, and 8. There were no ethnical or regional restrictions for participation because the patients were referred from different regions of Iran to these referral hospitals and were enrolled if the patient and his/her family could adhere to the trial plan.

Intervention

Eligible participants were equally randomized into 2 groups to receive either NAC (Hexal Pharmaceutical, Germany) or pla- AQ7 cebo, in addition to risperidone (Risperdal; Janssen Pharmaceuticals), which was administered to all patients. Starting dose of risperidone was 2 mg/d, which was increased weekly in increments of 2 mg, on the basis of clinical response, to a maximum dose of 6 mg/d (2 mg tid). The NAC initial dosage was 1000 mg/d AQ8 (500 mg bid) for the first week, followed by 2000 mg/d (1000 mg bid) for the subsequent 7 weeks. The patients were not allowed to receive any behavior intervention therapy during the course of the trial.

Outcomes

The PANSS was the efficacy assessment measure used in this study, and the patients were rated using PANSS on the basis of a structured clinical interview at baseline/screening session and weeks 2, 4, 6, and 8. The PANSS is a 30-item rating scale consisting of validated subscales to examine positive (7 items), negative (7 items), and general psychopathological (16 items) symptoms of schizophrenia. These 3 subscales are summed up in the PANSS total score.[29] The PANSS has been widely used for measuring the severity of symptoms in patients with schizophrenia

and has been applied in several studies in Iran.[30–35] The raters were previously involved in several trials of schizophrenia and had good experience in implementing the PANSS. Four trained raters were responsible for rating the patients with an interreliablity of greater than 90% on PANSS total symptoms. The HDRS was also filled at baseline and week 8 to assess changes in depressive symptoms. This scale contains 17 questions (measured either on 5-point or 3-point scales) that evaluate the severity of depression-related symptoms.[28] The primary outcome of this study was the difference in the decrease of PANSS negative subscale score from baseline to the study end point (week 8) between the 2 groups. The difference between the 2 study arms on other PANSS subscales and the PANSS total score were considered as secondary outcome measures.

Safety

A thorough physical examination was performed, and vital signs were recorded at the screening session and each post-baseline visit. The participants and the nurses were encouraged to immediately inform the research team about any unexpected symptom after entering the study. Adverse effects were recorded by a psychiatry resident at weeks 1, 2, 4, 6, and 8 through open-ended questioning, followed by a complete adverse effects checklist. The adverse effects checklist was a 25-item questionnaire covering a broad range of complaints. To evaluate the possible extrapyramidal symptoms, the Extrapyramidal Symptoms Rating scale (ESRS) (part 1: parkinsonism, dystonia, dyskinesia; sum of 11 items) was also administered at baseline and weeks 1, 2, 4, 6, and 8.[36] In case of encountering any adverse effect at any time, an expert psychiatrist was responsible to make decisions regarding whether to continue treatment, decrease dosage, or discontinue the drugs. The behavior appraisal and adverse effects checklist were completed by independent raters.

Randomization

The random allocation method was used to randomly and equally assign the participants to the NAC or the placebo group in a 1:1 ratio. Randomization codes were generated by means of Excel software by an independent person who was not involved elsewhere in the research project. The assignments were kept in sequentially numbered, sealed, opaque envelopes and were opened sequentially only after participant details were written on the envelope. The aluminum foil inside the envelope rendered the envelope impermeable to intense light. Separate persons were responsible for rating and random allocation of the patients.

Blinding

The participants, the nurses, and the physicians who referred the patients were all blind to the treatment assignments as well as to the research investigators and the raters. Placebo tablets and their ingredients were identical to NAC tablets in shape, size, texture, color, taste, and odor. The study drugs were packed in identical containers and were dispensed by an investigational drug pharmacist.

Statistical Methods and Sample Size

IBM SPSS Statistic 20 (IBM Corporation) was used for data analysis. The mean score changes on PANSS, HDRS, and ESRS from baseline to the study end point were compared between the 2 groups using independent sample t test. The effect of time and time × treatment interaction was assessed using the general

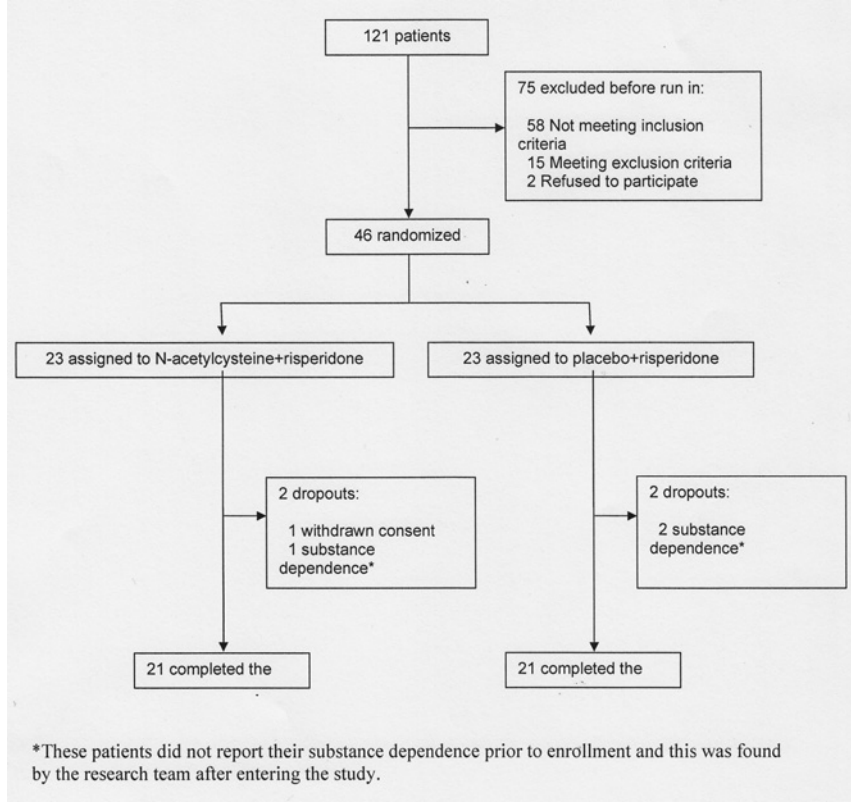

FIGURE 1. Flow diagram of the study.

linear model repeated measures considering the treatment group (NAC vs placebo) as the between-subject factor and the study measurements as the within-subject variables (time). If the Mauchly test of sphericity was significant, Greenhouse-Geisser correction for degrees of freedom was used. Multiple linear regression analysis was used to predict the change in PANSS negative subscale scores (as our primary outcome) by assigning change in PANSS positive subscale, HDRS, and ESRS scores as well as the treatment group. Categorical variables were described in number (%); continuous variables, as mean (SD). Mean differences (MDs) were reported as MD 95% confidence intervals (95% CI). A P value of less than 0.05 was considered statistically significant. On the basis of previous trials, we assumed a final difference of 5 between the 2 groups on the PANSS negative subscale with a standard deviation of 5, a power of 90%, a 2-sided significance level of 5%, and an attrition rate of 10%. Therefore, a total sample size of 46 was calculated.

RESULTS

Participants

One hundred and twenty-one patients were screened for the eligibility criteria, and 46 patients were randomized into 2 groups. Two patients from each group dropped out from the trial before week 2 because of either withdrawal of consent or substance dependence. A total number of 42 patients (placebo, 21; NAC, 21) completed the trial (Fig. 1). There was no significant difference between baseline characteristics of the patients, which are summarized in Table 1. Mean (SD) dose of the risperidone administered throughout the study was 4.20 (0.63) mg/d in the NAC group and 4.15 (0.56) mg/d in the placebo group. Baseline PANSS total and subscale scores were not significantly different between the 2 groups, as well as the baseline HDRS and ESRS scores (Table 2).

TABLE 1. Baseline Characteristics of the Participants

Variable	*N*-acetylcysteine + Risperidone	Placebo + Risperidone
Sex, n (%)		
Female	12 (57)	10 (48)
Male	9 (43)	11 (52)
Age, mean (SD), y	32.23 (6.12)	33.38 (6.97)
Marital status, n (%)		
Single	18 (86)	15 (71)
Married	3 (14)	5 (24)
Divorced	—	1 (5)
Level of education, n (%)		
Illiterate	1 (5)	—
Primary school	13 (61)	17 (80)
High school diploma	6 (29)	2 (10)
University degree	1 (5)	2 (10)
Smoking, n (%)	15 (71)	19 (90)
Duration of illness, mean (SD), mo	83.23 (41.02)	88.95 (44.66)
Type of schizophrenia, n (%)		
Paranoid	10 (47)	11 (53)
Residual	4 (19)	3 (14)
Disorganized	2 (10)	4 (19)
Undifferentiated	5 (24)	3 (14)
Prior antipsychotic medications, n (%)		
Risperidone	16 (76)	15 (21)
Halopridol	11 (52)	14 (67)
Fluphenazine	6 (29)	7 (33)
Olanzapine	6 (29)	3 (14)

Outcomes

Positive and Negative Syndrome Scale

The PANSS Negative Subscale

The NAC group showed significantly greater improvement in the negative symptoms than that in the placebo group by the end of the trial (MD 95% CI, 6.61 [4.08–9.15]; $t_{40} = 5.27$; $P < 0.001$). In repeated-measure analysis, the effect of time was significant ($F_{1.95,78.15} = 170.62$, $P < 0.001$). The behavior of the 2 treatment groups was not similar across time as demonstrated by a significant effect for time × treatment interaction ($F_{1.95,78.15} = 16.64$, $P < 0.001$) (Fig. 2). When the PANSS negative subscale change was predicted by multiple linear regression analysis, it was found that the treatment group ($\beta = -0.64$, $t = -5.23$, $P < 0.001$) and the change in HDRS ($\beta = 0.24$, $t = 2.04$, $P = 0.04$) were independent significant predictors. Changes in the PANSS positive subscale ($\beta = 0.05$, $t = 0.42$, $P = 0.67$) and ESRS ($\beta = 0.05$, $t = 0.43$, $P = 0.66$) scores could not significantly predict the change in PANSS negative subscale scores. Treatment group (NAC or placebo) was the strongest predictor of any negative symptom changes over the course of this trial.

The PANSS Positive Subscale

Reduction of the scores in the PANSS positive subscale was not significantly different between the 2 groups at the end of the trial (MD 95% CI, −0.95 [−4.38 to 2.48]; $t_{40} = -0.56$; $P = 0.57$). The results of repeated-measure analysis revealed a significant effect for time ($F_{2.56,102.49} = 240.11$, $P < 0.001$) but not for time × treatment interaction ($F_{2.56,102.49} = 0.90$, $P = 0.42$), showing that the behavior of the 2 groups was similar across time.

The PANSS General Psychopathology Subscale

No significant difference was determined in the reduction of PANSS general psychopathology subscale scores between the 2 groups by week 8 (MD 95% CI, 6.00 [−0.28 to 12.28]; $t_{40} = 1.93$; $P = 0.06$]. The effect of time was significant in the repeated-measure analysis ($F_{1.71,68.72} = 142.98$; $P < 0.001$), but the effect of time × treatment interaction was not significant ($F_{1.71,68.72} = 2.99$; $P = 0.06$), showing that the behavior of the 2 groups was similar across time.

The PANSS Total Score

At the study end point, the patients in the NAC group experienced significantly greater improvement in the PANSS total scores than that in the placebo group (MD 95% CI, 11.66 [3.62 to 19.71]; $t_{40} = 2.93$; $P = 0.006$]. The results of the repeated-measure analysis showed significant effect for time ($F_{2.00,80.29} = 378.91$, $P < 0.001$] and time × treatment interaction ($F_{2.00,80.29} = 5.48$, $P = 0.006$).

The Hamilton Depression Rating Scale

There was no significant difference between the 2 groups in the HDRS score change from baseline to the study end point (MD 95% CI, −0.04 [−0.48 to 0.39]; $t_{40} = -0.21$; $P = 0.82$).

TABLE 2. Mean (SD) Scores of the 2 Groups on Different Study Measures

Measure	Week	*N*-acetylcysteine + Risperidone	Placebo + Risperidone	*P*	Time × Treatment Interaction
PANSS Negative subscale, mean (SD)	Week 0	27.38 (4.35)	27.28 (6.10)	0.95	**$P < 0.001$**
	Week 2	23.80 (3.84)	25.58 (6.34)	0.21	
	Week 4	19.71 (3.59)	23.66 (6.96)	**0.02**	
	Week 6	17.61 (3.61)	21.85 (7.29)	**0.02**	
	Week 8	14.04 (2.51)	20.57 (7.99)	**0.001**	
PANSS Positive subscale, mean (SD)	Week 0	30.23 (3.68)	32.33 (5.48)	0.15	$P = 0.42$
	Week 2	25.95 (3.59)	25.90 (4.99)	0.97	
	Week 4	21.04 (3.15)	21.09 (4.54)	0.96	
	Week 6	16.38 (2.06)	16.71 (3.56)	0.71	
	Week 8	12.19 (3.37)	13.33 (4.56)	0.36	
PANSS General psychopathology subscale, mean (SD)	Week 0	55.80 (8.36)	55.00 (6.13)	0.72	$P = 0.06$
	Week 2	51.28 (8.52)	50.76 (5.89)	0.81	
	Week 4	43.47 (7.21)	44.14 (7.68)	0.77	
	Week 6	37.04 (6.98)	40.14 (8.29)	0.19	
	Week 8	31.09 (9.09)	36.28 (7.59)	0.05	
PANSS Total score, mean (SD)	Week 0	113.42 (9.05)	114.61 (10.09)	0.69	**$P = 0.006$**
	Week 2	101.04 (10.44)	102.52 (7.83)	0.60	
	Week 4	84.23 (10.31)	88.90 (10.10)	0.14	
	Week 6	71.04 (9.00)	78.71 (12.20)	**0.02**	
	Week 8	57.33 (10.45)	70.19 (12.46)	**0.001**	
HDRS, mean (SD)	Week 0	8.28 (1.92)	8.09 (1.84)	0.74	$P = 0.82$
	Week 8	8.14 (1.68)	7.90 (1.70)	0.65	
ESRS, mean (SD)	Week 0	1.00 (2.52)	0.90 (2.71)	0.90	$P = 0.64$
	Week 1	3.80 (4.13)	5.19 (4.63)	0.31	
	Week 2	6.00 (7.28)	6.90 (4.54)	0.63	
	Week 4	4.09 (2.68)	5.76 (3.85)	0.11	
	Week 6	2.52 (2.50)	4.47 (3.95)	0.06	
	Week 8	1.71 (1.38)	2.95 (2.72)	0.07	

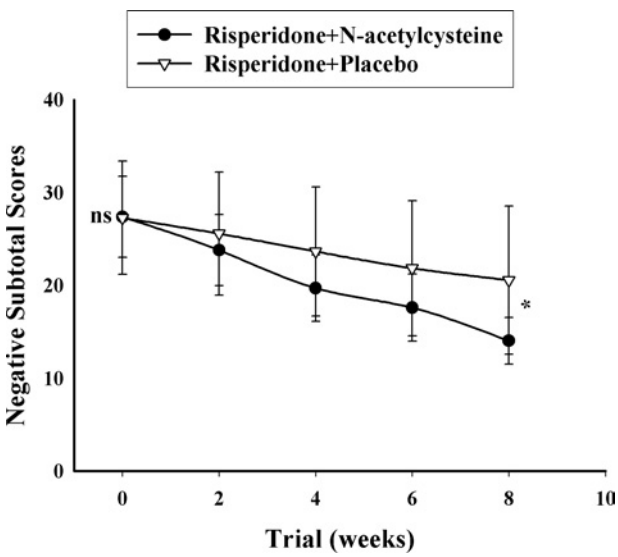

FIGURE 2. Comparison of the negative subscale scores of PANSS (mean [SD]) over time between the 2 study groups. The asterisk symbol indicates $P < 0.05$.

The results of the repeated-measure analysis did not show significant effect neither for time ($F_{1.00,40.00} = 2.35$, $P = 0.13$) nor for time × treatment interaction ($F_{1.00,40.00} = 0.04$, $P = 0.82$].

Adverse Events

No serious adverse event or death was reported in this trial. Other than extrapyramidal symptoms assessed by ESRS, 10 adverse effects were observed over the course of the trial on the basis of the adverse effects checklist. No significant difference was detected between the 2 groups in the frequency of adverse effects (Table 3). T3

The Extrapyramidal Symptoms Rating Scale

There was no significant difference in the ESRS score changes from baseline to week 8 between the 2 study groups (MD 95% CI, 1.33 [−0.70 to 3.37]; $t_{40} = 1.31$; $P = 0.19$). The results of the repeated-measure analysis showed significant effect for time ($F_{2.96,118.70} = 16.29$, $P < 0.001$), but the effect of time × treatment interaction was not statistically significant ($F_{2.96,118.70} = 0.54$, $P = 0.64$) (Table 2).

DISCUSSION

In line with our hypothesis, we showed that NAC was effective and tolerable in treating the primary negative symptoms

TABLE 3. Frequency of the Adverse Effects in the 2 Study Groups

Adverse Effect	*N*-acetylcysteine + Risperidone	Placebo + Risperidone	*P*
Drowsiness, n (%)	7	4	0.48
Constipation, n (%)	4	3	1.00
Dizziness, n (%)	6	4	0.71
Vomiting, n (%)	5	2	0.40
Increased appetite, n (%)	4	4	1.00
Nausea, n (%)	6	3	0.45
Headache, n (%)	5	3	0.69
Dry mouth, n (%)	5	2	0.40
Increased blood pressure, n (%)	4	1	0.34
Diarrhea, n (%)	6	3	0.45

of schizophrenia. In this study, the patients receiving NAC showed significantly better improvement in the PANSS total and negative subscale scores, but there was no difference between the 2 groups in the PANSS positive or general psychopathology subscales, HDRS, or ESRS. Negative symptoms consist of those that are primary to schizophrenia and the so-called secondary negative symptoms, which are secondary to other manifestations of schizophrenia, as well as symptoms due to illness treatment.[1] To investigate the pure effect of medications on negative symptoms in clinical trials and to attribute the clinical response to improvement of primary negative symptoms, changes in confounding factors including positive, depressive, and extrapyramidal symptoms should be minimal during the course of the trial.[1,3] In the present study, no significant difference was detected in the positive, depressive, and extrapyramidal symptoms between the 2 groups. Hence, we can attribute the improvement of the negative symptoms in the NAC group to the reduction of primary negative symptoms. Moreover, we measured changes in extrapyramidal symptoms throughout the study and could find no significant difference in the ESRS scores between the 2 groups. No serious adverse effect was observed in the NAC group, and there was no significant difference between the 2 trial groups in this regard, further supporting the safety profile of NAC in these patients.

Several studies have investigated the beneficial effects of NAC on schizophrenic patients.[22,24,25,27,37,38] Lavoie et al[22,24,25,27,37,38] investigated the efficacy of NAC on cerebral functioning by means of a particular type of auditory evoked potentials called MMN, which is an indicator of deficits in NMDAR function. They showed that add-on NAC significantly improves MMN generation in patients with schizophrenia, implicating GSH dysregulation and glutamatergic dysfunction as potential therapeutic targets in schizophrenia.[25] In another randomized, double-blind, placebo-controlled trial, Berk et al reported that 2 g/d add-on NAC can be helpful in alleviating the schizophrenia-related symptoms during a 24-week period. Compared with the results of our study, they showed significant improvement in PANSS general psychopathology subscale, in addition to total and negative subscale scores. The mean difference of negative symptoms reduction by the end of week 24 between the 2 groups was less than 2 in their trial compared with the mean difference of 6.61 in our study. Taken together, these findings suggest that short-term therapy with adjunctive NAC may have the same efficacy as that of long-term therapy in the treatment of negative symptoms of schizophrenia. Improvement of negative subscale scores was observed in that study without any significant change in positive symptoms, but unlike our study, they also reported significant improvement of akathisia in the NAC group and suggested NAC as a neuroprotective agent for treatment of extrapyramidal symptoms as well. Of note, Berk et al[24] studied the effect of NAC on patients with stable chronic schizophrenia, whereas the patients in our study were in active phase of their illness (high degree of total psychopathology; PANSS total score, >60). Therefore, the differences between the results of the 2 studies on the improvement of negative symptoms with NAC therapy can be attributed to differences in studied populations or study designs that warrant further investigation to be clarified.

There are several reasons to explain why NAC can be helpful in treating schizophrenia. *N*-acetylcysteine is an acetylated derivative of amino acid L-cysteine. After an oral administration, NAC reaches brain glial cells and is then oxidized to cystine, which enters the cells in exchange for glutamate, leading to increased extracellular glutamate. The entered cystine is subsequently reduced to cysteine, acting as a GSH precursor and resulting in increased GSH levels.[21,23,39] Glutathione ultimately acts as a potent antioxidant and decreases cellular damage by scavenging reactive oxygen species.[6,8,40] In addition to GSH production enhancement, NAC itself has been shown to have direct radical scavenging properties as well.[41] This antioxidant property of NAC is particularly interesting in light of increasing evidence suggesting deficits in oxidative defenses in schizophrenia.[42,43] Besides affecting the oxidative balance, NAC has beneficial regulatory effects on some impaired neurotransmission pathways in schizophrenia including glutamate and dopamine. Glutathione directly potentiates brain NMDARs in the brain and indirectly regulates the neuronal glutamate exchange via cystine-glutamate antiporter.[16,44,45] Moreover, NAC has been shown to modulate the dopamine release from neuronal terminals as well.[46,47] The role of immune system dysregulation and alteration in inflammatory responses has been implicated in the pathophysiology of schizophrenia.[48] At least a part of NAC's favorable effects seems to be due to its anti-inflammatory properties and reduction of inflammatory cytokines.[23,49,50]

The results of this study should be interpreted with caution in light of its limitations. Small sample size and short observational period are the major limitations of our study and require the results to be confirmed in larger and more extended trials. Although PANSS is widely accepted and applied for evaluating treatment effects in schizophrenia research, the application of this tool limited our study to assessment of behavioral problems; hence, we could not evaluate the possible effects of NAC on cognitive functions in this study.[29] In conclusion, the present study showed that 8 weeks of NAC treatment as an adjunct to risperidone is safe and has significant beneficial effects in treatment of schizophrenia negative symptoms.

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